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Evaluation of the evidence on acetaminophen use and neurodevelopmental disorders using the Navigation Guide methodology

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Abstract

Background Acetaminophen is the most commonly used over-the-counter pain and fever medication taken during pregnancy, with > 50% of pregnant women using acetaminophen worldwide. Numerous well-designed studies have indicated that pregnant mothers exposed to acetaminophen have children diagnosed with neurodevelopmental disorders (NDDs), including autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD), at higher rates than children of pregnant mothers who were not exposed to acetaminophen.

Methods We applied the Navigation Guide methodology to the scientific literature to comprehensively and objectively examine the association between prenatal acetaminophen exposure and NDDs and related symptomology in offspring. We conducted a systematic PubMed search through February 25, 2025, using predefined inclusion criteria and rated studies based on risk of bias and strength of evidence. Due to substantial heterogeneity, we opted for a qualitative synthesis, consistent with the Navigation Guide's focus on environmental health evidence.

Results We identified 46 studies for inclusion in our analysis. Of these, 27 studies reported positive associations (significant links to NDDs), 9 showed null associations (no significant link), and 4 indicated negative associations (protective effects). Higher-quality studies were more likely to show positive associations. Overall, the majority of the studies reported positive associations of prenatal acetaminophen use with ADHD, ASD, or NDDs in offspring, with risk-of-bias and strength-of-evidence ratings informing the overall synthesis.

Conclusions Our analyses using the Navigation Guide thus support evidence consistent with an association between acetaminophen exposure during pregnancy and increased incidence of NDDs. Appropriate and immediate steps should be taken to advise pregnant women to limit acetaminophen consumption to protect their offspring's neurodevelopment.

Keywords ADHD, ASD, Neurodevelopmental, Acetaminophen, Pregnancy

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Background

Pregnancy is a critical period—the embryonic and fetal stages are times of rapid and sequential physiological and developmental changes. The developing brain is especially vulnerable to environmental exposures because of incomplete development of the blood–brain barrier and the ongoing growth, differentiation, and pruning of neurons throughout early childhood. The complex and tightly regulated nature of brain development in utero means that even minor or temporary disruptions to the process can have significant and long-lasting effects on the developing brain. Thus, early exposures to chemicals, toxicants, pharmacologic agents, and other exogenous agents can alter normal neurodevelopment and have long-lasting effects, including neurodevelopmental disorders (NDDs) [1].

NDDs describe a category of conditions that result from deviations in normal brain development, resulting in a wide variety of symptoms that may include difficulties in areas such as learning, social and motor skills, attention, cognition, emotions, and behavior. While the causes of NDDs are often rooted in pregnancy[2], these disorders typically manifest and are diagnosed during childhood, when the function of the child's brain appropriate for a developmental stage can be assessed. NDDs include autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD). ASD affects communication and social interaction; ADHD affects attention and behavior, and affected children show hyperactivity and impulsivity. Different NDDs often have shared/overlapping symptomology as well as shared biological pathways or causes, including toxic exposures during critical developmental windows [3] or genetic causes [4]. A range of prenatal and early-life environmental factors—including, but not limited to, medication use—remain under investigation as potential contributors. However, population-level time trends, which may be influenced by improved diagnostic tools and awareness, cannot establish causation for any single exposure, such as acetaminophen, and may raise the risk of ecological fallacy[5]. Therefore, this review, using the Navigation Guide methodology, focuses on individual-level evidence linking prenatal acetaminophen use with neurodevelopmental outcomes.

Acetaminophen (also known as paracetamol) is currently considered the only pain and fever reducer indicated for use during pregnancy because of the risks of miscarriage or birth defects associated with other analgesics in common use [6]. In fact, associations such as the American College of Obstetricians and Gynecology have reassured patients that acetaminophen is safe to take during pregnancy [7]. Thus, acetaminophen has become the first-line medication for fever and pain during pregnancy. It has been estimated that > 60% of women use acetaminophen during pregnancy for headaches and other pain, or fever, with ~ 20% of pregnant women using acetaminophen for > 20 days [8].

Previous systematic reviews and meta-analyses[10–15], have examined the association between prenatal acetaminophen exposure and neurodevelopmental disorders (NDDs). Still, the Navigation Guide methodology offers a rigorous, transparent framework designed for observational studies. Thus, here we applied the Navigation Guide to analyze the available scientific literature to comprehensively assess the influence of prenatal use of acetaminophen on the developing brain and specifically to determine whether prenatal use of acetaminophen causes NDDs including ADHD, ASD, and other symptoms consistent with those disorders in children. The Navigation Guide requires systematic rating and review of each identified study for bias, strength of evidence, and study quality. Thus, we believe that applying the Navigation Guide was fitting to systematically and objectively review the literature on prenatal acetaminophen use and the development of NDDs.

Methods

Study selection

We conducted a systematic PubMed search of the literature on February 2–25, 2025, to identify original papers on the relationship between ADHD/ASD/NDDs and prenatal exposure to acetaminophen, including observational studies and meta-analyses. PubMed was selected as the primary database for its comprehensive coverage of biomedical and environmental health literature, aligning with the study's focus on prenatal acetaminophen exposure and neurodevelopmental disorders. To ensure completeness, supplementary searches were conducted in ISI Web of Science and Google Scholar using identical keyword strategies (e.g., 'ADHD AND acetaminophen'). These confirmed the inclusion of all relevant studies, with no additional eligible studies identified beyond those captured in PubMed. To guide study selection, we defined the research question using a Population, Exposure, Comparator, Outcome—PECO framework: Population: offspring of pregnant women assessed for neurodevelopmental outcomes; Exposure: prenatal acetaminophen (paracetamol) exposure, measured via maternal self-report, biomarkers, or medical records; Comparator: offspring of pregnant women not exposed to acetaminophen or exposed to alternative analgesics; Outcome: neurodevelopmental disorders, including ADHD, ASD, or related symptoms, diagnosed or assessed in childhood. Eligible studies were original observational studies (e.g., cohort, case–control) published in peer-reviewed journals, focusing on prenatal acetaminophen exposure

and NDD outcomes. We excluded studies on postnatal exposures, non-human studies (in vitro or animal) for the primary analysis, and duplicates or non-original research (e.g., reviews, editorials). To avoid duplication of evidence, we excluded studies presenting results from the same cohort or dataset. When multiple articles used the same data, reviewers retained the study with the largest sample size, the most complete reporting of exposure and outcome data, and/or the highest methodological quality, based on the Navigation Guide's risk-of-bias assessment. This ensured that only the most robust and representative study from each dataset was included. Titles and abstracts retrieved from the PubMed search were independently screened by two authors to assess eligibility based on predefined criteria. Disagreements were resolved through discussion; if unresolved, a third reviewer adjudicated to ensure consensus. A fourth reviewer updated the methodology, verified study selections, and confirmed result accuracy, aligning with the Navigation Guide's structured evaluation framework.

Acetaminophen and ADHD

We used the search term "ADHD AND acetaminophen." Using additional search terms, such as "attention-deficit/hyperactivity disorder," "paracetamol," or "Tylenol," did not identify any additional results. A total of 96 papers were identified (the initial PUBMED search yielded 94 papers, and two additional papers were identified when reviewing the PUBMED search[16] and during Google Scholar confirmation[17]. The exclusion of papers not related to ADHD and prenatal acetaminophen exposure yielded 70 relevant papers: 6 in vitro or animal studies, 18 original (20 total with separate analysis of sibling cohorts) non-duplicative studies in humans, 4 meta-analyses, 28 reviews or studies that duplicated or elaborated on previously published original studies in humans, and 14 editorials or comments (Fig. 1, left).

Acetaminophen and ASD

We used the search term "(autism spectrum disorder OR autism OR ASD) AND acetaminophen." Using additional search terms, such as "paracetamol" or "Tylenol", did not return any additional results. The initial search yielded 114 papers. The exclusion of papers not related to ASD and prenatal acetaminophen exposure yielded 63 relevant papers: 13 in vitro or animal studies, 7 original, non-duplicative studies in humans (8 with separate analysis of sibling cohort), 1 meta-analysis, 30 reviews or studies that duplicated or elaborated on previously published original studies in humans, and 12 editorials or comments (Fig. 1, center).

Acetaminophen and other neurodevelopmental deficits/disorders

We used the search term "(neurodevelopment OR neurodevelopmental disorder OR brain development) AND acetaminophen." Using additional search terms, such as "paracetamol" or "Tylenol," did not return any additional results. The initial search yielded 308 papers. To avoid overlapping with the other searches, papers related to ADHD or ASD were excluded. Exclusion of papers not related to neurodevelopment and prenatal acetaminophen yielded 69 relevant papers: 24 in vitro or animal studies, 17 original studies in humans (18 with separate analysis of sibling cohort), 17 reviews, and 11 editorials or comments (Fig. 1, right).

Exclusion criteria

After identifying relevant studies with the above search criteria, we excluded studies that presented results from the same data and were published in two different journals with slight differences.

Data extraction and quality assessment

We used standardized Navigation Guide methodology to extract and evaluate data from the identified studies, including publication year, study design, number of cases, number of controls (for case–control studies), total sample size (for cohort studies), population type, country, risk estimates, confidence intervals, and type of NDD. We also indicated if exposure–response relationships were assessed, as well as the method used, and the resulting effect estimates and 95% Confidence Intervals (CIs). After extracting data, papers were evaluated and synthesized to identify patterns, themes, and trends across studies.

Summary of assessments

We used the Navigation Guide methodology to rate studies based on several metrics. The risk of bias within each study was assessed using the GRADE approach to grade study characteristics that can introduce systematic errors in the magnitude or direction of the results. We rated each study for risk of bias, including participant recruitment/selection, blinding during the study, exposure assessment methods, outcome assessment methods, methods to address incomplete data, selective outcome reporting, and conflict of interest. We ranked each study on each parameter: 1 indicated low risk of bias, 2 indicated probably low risk of bias, 3 indicated probably high risk of bias, and 4 indicated high risk of bias. We calculated an average bias score for each study. For the

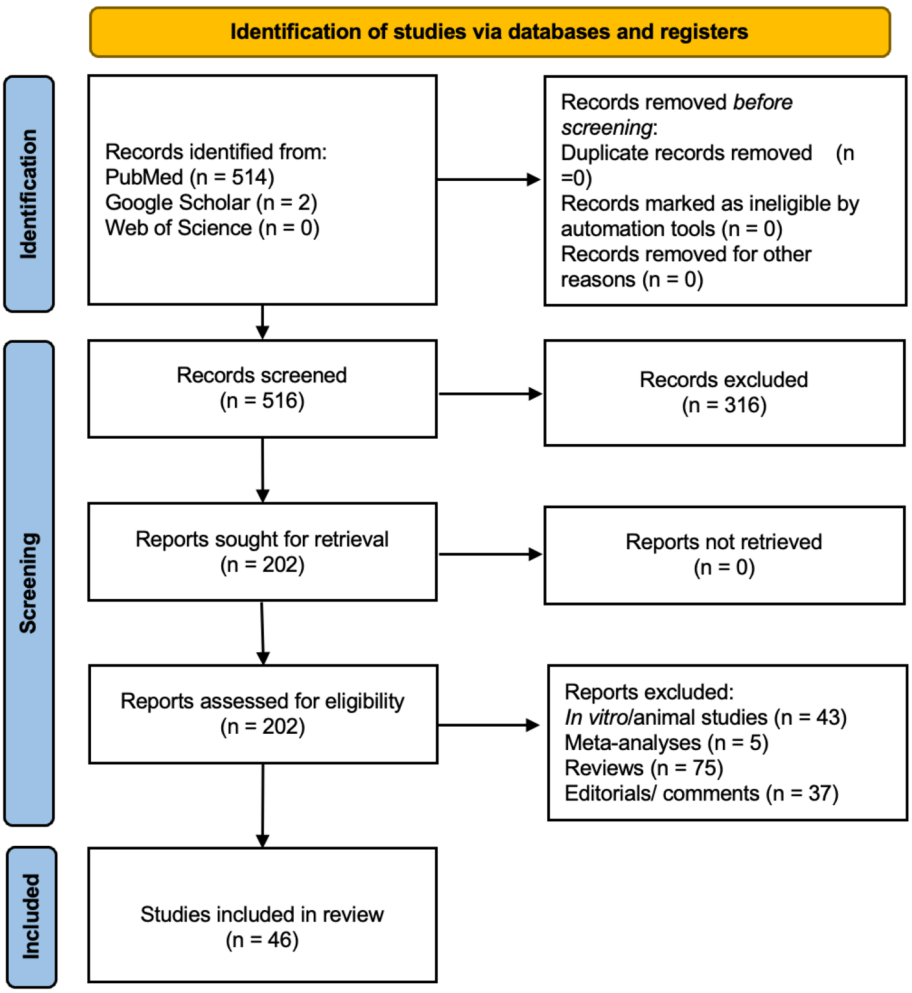

Fig. 1 PRISMA Flowchart of Study Selection. This figure illustrates the identification ($n = 516$), screening, eligibility assessment, and inclusion ($n = 46$) of studies, with exclusions detailed for in vitro/animal studies ($n = 43$), meta-analyses ($n = 5$), reviews ($n = 75$), and editorials/comments ($n = 37$), aligning with the Navigation Guide's systematic approach

'blinding during the study' domain, observational studies were rated as high risk of bias (score of 4) when knowledge of the outcome could influence exposure reporting. For instance, retrospective studies relying on maternal self-reports of acetaminophen use collected after a child's neurodevelopmental disorder diagnosis were rated high risk due to potential recall bias. Prospective designs or biomarker-based assessments mitigated this bias in higher-quality studies.

Deviations from scoring—such as inconsistencies in study methodology, incomplete data reporting, or challenges in applying bias criteria—were addressed through a structured process. During the study selection and data extraction phase, studies were triaged by title, abstract, and full text; two reviewers (AB and DP) independently assigned a score for each Navigation Guide category. Any deviations, such as studies with atypical designs or potential biases, were flagged for further evaluation. To handle these deviations, we conducted sensitivity analyses to assess their impact on the overall findings. Specifically, we performed two analyses: (1) excluding the lowest-scoring studies to evaluate their influence on the results, and (2) re-weighting confounding domains to address potential bias over- or underestimation.

Within the Navigation Guide's risk-of-bias assessment, confounding, including confounding by indication, was systematically evaluated. Studies were rated as higher risk of bias (score of 3 or 4) if they lacked adjustment for key confounders, such as maternal age, chronic illness, socioeconomic status, smoking, alcohol use, or clinical indications for acetaminophen use (e.g., fever or infection). We also assessed whether studies used sensitivity analyses, negative control exposures, or propensity score matching to address

confounding by indication, incorporating these evaluations into the overall risk-of-bias score for each study.

The Navigation Guide may also have additional limitations, including its numeric risk-of-bias scale. By assigning equal weight to every domain, the score can imply unwarranted precision and may fail to distinguish studies with minor shortcomings from those with major threats, particularly when confounding and exposure misclassification bias effects in opposite directions. For instance, in our analysis, confounding and exposure misclassification could bias results in opposing directions, yet the equal weighting of domains may not adequately distinguish studies with minor methodological flaws from those with significant threats to validity. In addition, there is still no consensus on the optimal set of domains for human observational research, nor on how to rate analytical choices (e.g., modelling strategy) as a separate source of bias. To partially address this concern, we conducted sensitivity analyses, including removing the lowest-scoring studies and re-weighting confounding domains twofold, facilitating the interpretation of scores. Finally, the Navigation Guide's default classification of observational evidence as "moderate" quality may skew final certainty ratings, particularly when integrating diverse study designs. To mitigate these limitations, we employed a triangulation framework, integrating findings from multiple study types to strengthen causal inference.

Following recommendations on causal inference in environmental epidemiology[18], we set our findings within a triangulation framework: when distinct study designs that suffer different, ideally opposing, biases reach congruent results, causal inference is strengthened. Our analysis integrates (i) prospective cohorts susceptible to residual confounding but strong temporality, (ii) biomarker-based studies with low recall bias but possible misclassification of dose, and (iii) experimental models largely free of confounding yet limited in external validity. The convergence of these independent sources of evidence increases confidence that the observed associations are not artefactual.

While a meta-analysis could provide quantitative synthesis, we opted against it due to significant heterogeneity in exposure assessment, outcome measures, and confounder adjustments across the studies evaluated. This variability, combined with non-comparable effect estimates, risked biased pooled results. Instead, the Navigation Guide methodology's qualitative synthesis, supported by risk-of-bias scoring and evidence triangulation, was deemed more suitable for evaluating the association between prenatal acetaminophen exposure and NDDs.

Results

Navigation guide workflow

To ensure rigor and transparency in applying the Navigation Guide methodology, we first defined a specific, answerable question: Is acetaminophen exposure during pregnancy associated with ADHD, ASD, or other neurodevelopmental disorders in the offspring? We then conducted a comprehensive literature search to identify relevant studies, using predefined inclusion and exclusion criteria to ensure consistency. Subsequently, we critically appraised the identified studies for quality and potential biases, including confounding factors (e.g., maternal indication, substance use, child age and sex, maternal age at delivery, maternal race/ethnicity, maternal educational level, marital status, stress during pregnancy, smoking before or during pregnancy, alcohol use before or during pregnancy, maternal, body mass index, parity, breastfeeding, ever use of illicit drugs, maternal fever during pregnancy, delivery type, preterm birth, and birth weight, etc.), to determine their reliability. After integrating findings from individual studies, we considered the strength and consistency of the evidence across different research designs. Finally, we rated the body of evidence based on factors such as study quality, consistency, and directness, following a structured approach. The Navigation Guide's risk-of-bias assessment included evaluating confounding factors (e.g., maternal age, socioeconomic status). Some of them could also be potential mediators of the relationships (e.g., delivery type, preterm birth, birthweight)[18], on neurodevelopmental outcomes. However, the complexity of these relationships requires additional evidence and goes beyond the current analysis. This systematic process aligns with the Navigation Guide's framework for synthesizing environmental health research.

Overview of the search results

Our literature search and application of study inclusion/exclusion criteria yielded a total of 46 studies included in this analysis with the addition of four separate sibling-controlled study analyses; this breaks down to: 20 studies of prenatal acetaminophen use and ADHD, 8 studies of prenatal acetaminophen use and ASD, and 18 studies of prenatal acetaminophen use and other NDDs. The search identified studies that found a statistically significant increased risk of NDDs such as ADHD and ASD from prenatal acetaminophen exposure, as well as a smaller number of studies that did not find such an association.

Study characteristics

Study characteristics are shown in Table 1 (ADHD) [16–35], Table 2 (ASD) [21], and Table 3 (other NDDs) [27–51]. Study designs included prospective cohort

Table 1 Characteristics of studies on prenatal acetaminophen use and attention-deficit/hyperactivity disorder (ADHD)

Authors, Year	Location	Study Period	Risk Estimate	Study Design	Sample Size	Missing Data	Inclusion Criteria	Exposure Definition	Outcome Definition
Ahlqvist, 2024 (overall study)	Sweden	1995–2019	HR = 1.07 (95%CI 1.05–1.07)	Prospective cohort	*N* = 2,480,797	Exclusion and Covariates imputed using dummy category approach	All Singleton live born children in Sweden with linkable personal identifiers with follow-up until Dec 31,2021	Ever use APAP derived from midwife interview at 8–10 weeks gestation and later during pregnancy. From 2005 onward supplemented by Prescribed Drug Registry data	ADHD from ICD codes recorded in the National Patient Registry. Use of ADHD medication from Prescribed Drug Registry
Ahlqvist, 2024 (sibling -controlled study)	Sweden	1995–2019	HR = 0.98 (95% CI 0.94–1.02)	Prospective cohort	*N* = 31,156 siblings discordant on exposure and outcome	Exclusion and Covariates imputed using dummy category approach	All Singleton live born children in Sweden with linkable personal identifiers with follow-up until Dec 31,2021	Ever use APAP derived from midwife interview at 8–10 weeks gestation and later during pregnancy. From 2005 onward supplemented by Prescribed Drug Registry data	ADHD from ICD-9 codes recorded in the National Patient Registry. Use of ADHD medication from Prescribed Drug Registry
Alemany, 2021	United Kingdom, the Netherlands, Denmark, Italy, Spain, and Greece	Pregnancies: 1991–2008	OR = 1.21 (95% CI: 1.07–1.36)	Prospective cohort	*N* = 73,881	Used cohort-specific criteria	Mother–children with available data on either prenatal or postnatal exposure to acetaminophen and at least one outcome (ADHD or ASD)	Mothers were interviewed 2–4 times during pregnancy using standardized questionnaires	Subscale of CBCL11/2–5 and CBCL6/18, and ADHD criteria of DSM-IV (DSM-ADHD questionnaire)
Avella-Garcia, 2016	Spain	Births 2004–2007	IRR = 1.25 (95% CI: 0.93–1.69) for ADHD IRR = 1.41 (95% CI: 1.01–1.98) for attention/impulsivity symptoms	Prospective cohort	*N* = 1,382	NA	Residents in the cohort area, ≥ 16 years old, singleton pregnancy, planning to give birth at the reference hospital	Maternal self-reports of acetaminophen use collected at weeks 12 and 32 of pregnancy	In-person evaluation using ADHD criteria of the DSM-IV at a mean age of 4.8 years to identify hyperactivity/inattention symptoms

Table 1 (continued)

Authors, Year	Location	Study Period	Risk Estimate	Study Design	Sample Size	Missing Data	Inclusion Criteria	Exposure Definition	Outcome Definition
Baker, 2020	Sherbrooke, Canada	Births: 2008–2010	OR = 2.43 (95% CI: 1.41–4.21) Dose response: 10% higher odds for each doubling of acetaminophen in meconium	Prospective cohort	*N* = 345	Missing covariate data were imputed with the median of continuous variables and the mode of categorical variables	Women ≥ 18 years old with no known thyroid disease	Measurement of acetaminophen in meconium samples	Parent-reported physician diagnosis of ADHD or diagnosis from medical records at 6–7 years of age
Baker, 2025	Tennesse, USA	2006–2011	aOR = 3.15 (95% CI 1.20–8.29) ADHD diagnosis aOR = 5.20 (1.48–18.28) ADHD medications	Prospective cohort	*N* = 307	Imputed using multivariate imputation by chained equations (MICE R package)	16–40 yr old female in Shelby Co., pregnant between 16–28 weeks, English speaking, singleton pregnancy, low risk. who self-identified as Black/African American. Randomly selected for untargeted metabolomics of 2nd trimester maternal plasma. Inclusion required ADHD data at age 8–10	Maternal plasma biomarkers of APAP exposure obtained during 2nd trimester	Parent reported ADHD diagnosis and ADHD medication use. Parent administered Child Behavior Checklist (CBCL). NIH Flanker and DIgital Span
Chen, 2019	Taiwan, nationwide	Births: 1998–2008	Exposure in any trimester: OR = 1.20 (95% CI: 1.01–1.42) Exposure in second trimester: OR = 1.19 (95% CI: 1.00–1.40) Exposure in first and second trimesters: OR = 1.28 (95% CI: 1.00–1.64)	Nested case–control study	950 study pairs and 3,800 control pairs (mothers–children without ADHD)	No missing data (national mandatory database)	Cases: diagnoses of ADHD by board-certified psychiatrists Controls: randomly (1:4) identified and matched by children's sex and age, mothers' age during pregnancy, income, and urbanization level	Prescriptions from the National Taiwan database; over-the-counter use and adherence to prescription was not captured	ADHD from ICD-9 codes recorded in the Taiwan Health Insurance Database

Table 1 (continued)

Authors, Year	Location	Study Period	Risk Estimate	Study Design	Sample Size	Missing Data	Inclusion Criteria	Exposure Definition	Outcome Definition
Gustavson, 2021 (Overall Study)	Norway	Pregnancies: 1999–2008	Adjusted HR (aHR) for long-term exposure (≥ 29 days) = 2.02 (95% CI: 1.17–3.25) aHR for short-term exposure (1–7 days) = 0.87 (95% CI: 0.70–1.08) aHR for short-term exposure (8–28 days) = 0.87 (95% CI: 0.70–1.08)	Cohort	*N* = 26,613	Exclusion	Pregnant women from across Norway were invited to their routine ultrasound examination at gestational week 17	Maternal questionnaires at gestational weeks 17 and 30	Hyperkinetic disorder (F90) according to 10th revision of the International Classification of Diseases (World Health Organization, 1993)
Gustavson, 2021 (sibling controlled study; controlled for family effect)	Norway	Pregnancies: 1999–2008	aHR in the sibling control model for long-term exposure (≥ 29 days), adjusted by family effect = 1.06 (95% CI: 0.51–2.05) at within-family level	Cohort	Only discordant siblings contributed to power; siblings were discordant on exposure for 29 days and the outcome in 34 families; total number of discordant siblings on exposure was 306	Exclusion	Pregnant women from across Norway were invited to their routine ultrasound examination at gestational week 17	Maternal questionnaires at gestational weeks 17 and 30	Hyperkinetic disorder (F90) according to 10th revision of the International Classification of Diseases (World Health Organization, 1993)
Ji, 2020	Boston, MA	Births: 1998–	Reference: Lowest tertile 2nd tertile: OR = 2.26 (95% CI: 1.40–3.69) 3rd tertile: OR = 2.86 (95% CI: 1.77–4.67)	Prospective cohort	*N* = 996	Missing data for sociodemographic characteristics (< 4%) imputed using multiple imputation by chained equations with predictive mean matching method	Mothers who delivered singleton live births at Boston Medical Center, excluding conception via in vitro fertilization, deliveries induced by maternal trauma, or newborns with major birth defects	Measurement of acetaminophen in cord blood samples (fetal blood)	Diagnosis from electronic medical records through average of 9.8 years of age

Table 1 (continued)

Authors, Year	Location	Study Period	Risk Estimate	Study Design	Sample Size	Missing Data	Inclusion Criteria	Exposure Definition	Outcome Definition
Liew, 2014	DENMARK nationwide	Pregnancies: 1996–2002	RRs for total SDQ > 16: RR = 1.13 (95% CI: 1.01–1.27) (any acetaminophen use) RR = 1.24 (95% CI: 1.03–1.48) (use in all three trimesters) HRs for hospital-diagnosed hyperkinetic disorder: RR = 1.37 (95% CI: 1.19–1.59) (any acetaminophen use) RR = 1.61 (95% CI: 1.30–2.01) (use in all three trimesters) ADHD medication: HR = 1.29 (95% CI: 1.15–1.44) (any acetaminophen use) HR = 1.44 (95% CI: 1.21–1.72) (use in all three trimesters)	Prospective cohort	*N* = 64,322	Multiple imputation	Pregnant women from ~ 50% of all general practitioners in Denmark; women who spoke insufficient Danish or did not intend to complete their pregnancy were excluded	Maternal self-reports during pregnancy collected via three telephone interviews	Parent's Standardized Strengths and Difficulties Questionnaire (SDQ) at age 7 years; hospital diagnosis of hyperkinetic disorders (ICD10: F90.0–F90.9); use of ADHD medications in the Danish Prescription Registry
Liew, 2016	Denmark	Births: 1996–2002	OR = 1.5 (95% CI: 1.0–2.5) for subnormal overall attention OR = 1.5 (95% CI: 1.0–2.4) for selective attention difficulties OR = 1.5 (95% CI: 0.9–2.3) for parent-rated subnormal executive function No significant associations with executive function	Prospective cohort	*N* = 1,491	Inverse probability weights to account for refusals to participate	Multiple imputations to address missing covariate values in all analyses (< 4% with at least one missing value)	Maternal self-reports at gestational weeks 12 and 30 and 6 months postpartum	At 5 years of age, trained psychologists assessed child's attention using the Test of Everyday Attention for Children at Five (TEACh-5); parents and preschool teachers completed Behaviour Rating Inventory of Executive Function (BRIEF)

Table 1 (continued)

Authors, Year	Location	Study Period	Risk Estimate	Study Design	Sample Size	Missing Data	Inclusion Criteria	Exposure Definition	Outcome Definition
Liew, 2019	Boston, MA	Births: 1993–2005	OR = 1.34 (95% CI: 1.05–1.72)	Prospective cohort	*N* = 8,856	No details included in the paper	Participants in the Nurses Health Study II who were asked to fill out a medication use questionnaire on the same year they were pregnant	Maternal self-report of regular acetaminophen use during the year of the child's birth	Maternal report of ADHD diagnosis in 2013
Stergiakouli, 2016	Avon, UK	Births: 1991–1992	RR = 1.27 (95% CI: 1.05–1.53) (18-week assessment) RR = 1.43 (95% CI: 1.18–1.73) (32-week assessment)	Prospective cohort	*N* = 7,996	Addressed using inverse-probability-weighting (< 1% missing)	Pregnant women living in Avon, UK, with expected delivery dates from April 1991–December 1992	Maternal self-reports of acetaminophen use in the previous three months collected at 18 and 32 weeks of pregnancy	Strength and Difficulties Questionnaire (SDQ) at age 7 years
Streissguth, 1987	Seattle, WA	Pregnancies: 1974–1975	β = −3.25; SE = 6.92; p = 0.64 for the association between acetaminophen use in the first half of pregnancy and attention score used in the study	Prospective cohort	*N* = 355	Exclusion	Consecutive group of women seeking prenatal care	Maternal self-reports at 5th month of pregnancy	Attention tested with a vigilance paradigm (Streissguth, 1984)
Sznajder, 2022	Pennsylvania, USA	Births: 2009–2011	OR = 1.21 (95% CI: 1.01–1.45)	Prospective cohort	*N* = 2400	Individual mean imputation of missing outcomes measures (< 2%)	Nulliparous pregnant women in the third trimester, 18–35 years, English or Spanish speaking, planning to deliver at a hospital in Pennsylvania, no plans for the child to be adopted, and delivering at ≥ 34 weeks gestation	Self reports of medication use during pregnancy in third trimester phone inteview; dose and frequency were queried but not used in the analysis	Attention problems from the Child Behavior Checklist (CBCL) at age 3 years (> 80th percentile of the scale)
Thompson, 2014	Auckland, Australia	Births: 1995–1997	β = 1.1 (0.2, 2.0) for parent SDQ at 7 years β = 0.8 (−0.1, 1.8) for parent SDQ at 11 years β = 1.1 (0.2, 2.0) for child SDQ at 11 yrs	Prospective cohort	*N* = 871	NA	Only children born to mothers of European Ancestry were included	Maternal self-reports of acetaminophen use collected soon after delivery	Strength and Difficulties Questionnaire (SDQ) and Conner's Parent Rating Scale-Revised at age 7 and 11 years

Table 1 (continued)

Authors, Year	Location	Study Period	Risk Estimate	Study Design	Sample Size	Missing Data	Inclusion Criteria	Exposure Definition	Outcome Definition
Tovo-Rodrigues, 2018	Pelota, Brazil	Births: 2004	All subjects: OR = 1.10 (95% CI: 0.87–1.39) at 6 years OR = 1.20 (95% CI: 0.96–1.49) at 11 years Boys: OR = 1.42 (95% CI: 1.06–1.92) at 6 years OR = 1.31; 95% CI: 0.99–1.73 at 11 years	Prospective cohort	*N* = 3470 (age 6 analysis); *N* = 3447 (age 11 analysis)	No details included in the paper	All singleton live births in Pelota in 2044	Maternal self-report of acetaminophen use at post-delivery examination	Score ≥ 7 for inattention/hyperactivty symptoms on the Strengths and Difficulties Questionnaire, evaluated at age 6 and 11 years
Woodbury, 2024	Illinois, USA	Pregnancies:2013–2020	Per unit increase in APAP use in 2nd trimester β = 0.009 (95% CI 0.003–0.015) at 2 yrs, β = 0.009 (0.003- 0.015) at 3 yrs Throughout pregnancy, β = 0.004 (0.001- 0.008) at 2 yrs, B = 0.004 (0.001–0.007) at 3 yrs	Prospective cohort	*N* = 535	Exclusion	18–40 year old English speaking pregnant women invited at 1st prenatal visit, not yet 15 weeks gestation, no other children in cohort, resided nearby, carrying singleton, considered low risk, plan to remain in area until child's 1st birthday	Maternal interview at 6 time points. 5 during pregnancy and 1 at birth	Attention problems from the Child Behavior Checklist (CBCL) at age 2 & 3 years

Table 1 (continued)

Authors, Year	Location	Study Period	Risk Estimate	Study Design	Sample Size	Missing Data	Inclusion Criteria	Exposure Definition	Outcome Definition
Ystrom, 2017	Norway, nationwide	Pregnancies1999-2008	1 trimester use (HR = 1.07; 95% CI 0.96–1.19), 2 (HR = 1.22; 95% CI 1.07–1.38), 3 (HR = 1.27; 95% CI 0.99–1.63). 29 days + of use (HR = 2.20 (95% CI 1.50–3.24). Use for < 8 days HR = 0.90; 95% CI 0.81–1.00). Use for fever and infections for 22 to 28 days was associated with ADHD (HR = 6.15; 95% CI 1.71–22.05)	**Prospective Cohort (why are other Norwegian studies just "Cohort"?)**	112,973	Multiple imputation	Pregnant women from across Norway were invited to their routine ultrasound examination at gestational week 18	s. Acetaminophen use was available from 2 prenatal and 1 postnatal questionnaires. At week 18, week 30, and 6 months postpartum	An International Classification of Diseases, 10th Revision diagnosis of hyperkinetic disorder (F90.0, F90.1, F90.8, or F90.9) between 2008 and 2014 were identified as having ADHD. Hyperkinetic disorder requires the combination of inattentive and hyperactive symptoms, and as a result, hyperkinetic disorder is a subtype nested within the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition classification of ADHD

Table 2 Characteristics of studies on prenatal acetaminophen use and autism spectrum disorder (ASD)

Authors, Year	Location	Study Period	Risk Estimate	Study Design	Sample Size	Missing Data	Inclusion Criteria	Exposure Definition	Outcome Definition
Ahlqvist, 2024 (overall study)	Sweden	1995–2019	HR = 1.05 (95%CI 1.02–1.087)	Prospective cohort	*N* = 2,480,797	Exclusion and covariates imputed using dummy category approach	All Singleton live born children in Sweden with linkable personal identifiers with follow-up until Dec 31,2021	Ever use APAP derived from midwife interview at 8–10 weeks gestation and later during pregnancy. From 2005 onward supplemented by Prescribed Drug Registry data	Autism from ICD codes recorded in the National Patient Registry
Ahlqvist, 2024 (sibling -controlled study)	Sweden	1995–2019	HR = 0.98 (95% CI 0.93–1.04)	Prospective cohort	*N* = 16,267 siblings discordant on exposure and outcome	Exclusion and covariates imputed using dummy category approach	All Singleton live born children in Sweden with linkable personal identifiers with follow-up until Dec 31,2021	Ever use APAP derived from midwife interview at 8–10 weeks gestation and later during pregnancy. From 2005 onward supplemented by Prescribed Drug Registry data	Autism from ICD codes recorded in the National Patient Registry
Alemany, 2021	UK, the Netherlands, Denmark, Italy, Spain, and Greece	Pregnancies: 1991–2008	OR = 1.19 (95% CI: 1.07–1.33)	Prospective cohorts	*N* = 73,881	NA	Mothers–children with available data on either prenatal or postnatal exposure to acetaminophen and at least one outcome (ADHD or ASD)	Mothers were interviewed 2–4 times during pregnancy using standardized questionnaires; regarding postnatal acetaminophen exposure, mothers were interviewed or completed questionnaires about medication use in their children 1–2 times in the first 18 months of life of the child	Subscale of the CBCL11/2–5 and CBCL6/18, and ADHD criteria of DSM-IV (DSM-ADHD questionnaire)

Table 2 (continued)

Authors, Year	Location	Study Period	Risk Estimate	Study Design	Sample Size	Missing Data	Inclusion Criteria	Exposure Definition	Outcome Definition
Avella-Garcia, 2016	Spain	Births 2004–2007	IRR = 1.25 (95% CI: 0.93–1.69) for ADHD IRR = 1.41 (95% CI: 1.01–1.98) for attention/ impulsivity symptoms	Prospective cohort	*N* = 1.382	NA	Residents in the cohort area, ≥ 16 years old, singleton pregnancy, planning to give birth at the reference hospital	Maternal self-reports of acetaminophen use collected at weeks 12 and 32 of pregnancy	In-person evaluation using Childhood Autism Spectrum Test (CAST)13, which quantifies autism spectrum symptoms in children (each point represents one symptom, with a cut-off of ≥ 15 points having a 100% sensitivity and 97% specificity)
Ji, 2020	Boston, MA	Births: 1998–	Reference: Lowest tertile 2nd tertile: OR = 2.14 (95% CI: 0.93–5.13) 3rd tertile: OR = 3.62 (95% CI: 1.62–8.60)	Prospective cohort	*N* = 996	Missing data for sociodemographic characteristics (< 4%) imputed using multiple imputation by chained equations with predictive mean matching method	Mothers who delivered singleton live births at Boston Medical Center, excluding conception via in vitro fertilization, deliveries induced by maternal trauma, or newborns with major birth defects	Measurement of acetaminophen in cord blood samples (fetal blood)	Diagnosis from electronic medical records through average of 9.8 years of age
Leppert, 2019	Avon, UK	Births: 1991–1992	RR = 0.76 (95% CI: 0.51–1.13)	Prospective cohort	*N* = 7,786	Addressed using inverse-probability-weighting (< 1% missing)	Pregnant women living in Avon, UK, with expected delivery dates from April 1991–December 1992	Maternal self-report for first and second half of pregnancy; info was collected at visits during pregnancy and delivery	a) Being diagnosed with pervasive developmental disorder using questions from DAWBA questionnaire at 91 months or b) mother's self report
Liew, 2016	Denmark	Births: 1996–2002	HR = 1.19 (95% CI: 1.04–1.35) HR = 1.51 (95% CI: 1.19–1.92) for ASD with hyperkinetic symptoms HR = 1.06 (95% CI: 0.92–1.24) for other types of ASD	Prospective cohort	*N* = 64,322	Multiple imputation for missing values in covariates (< 5% of participants)	Pregnancies in 1996–2002, recruited at weeks 6–12; exclusion criteria were women who did not speak Danish or did not intend to carry their pregnancy to term	Maternal self-reports at gestational weeks 12 and 30 and 6 months postpartum	ASD hosptial admissions from the Danish National Hospital Registry Danish Psychiatric Central Registry

Table 2 (continued)

Authors, Year	Location	Study Period	Risk Estimate	Study Design	Sample Size	Missing Data	Inclusion Criteria	Exposure Definition	Outcome Definition
Saunders, 2019	Saint John, Canada	Not specified, Ethics Board approval in 2013–2014	Not provided, but not significant ($p = 0.66$)	Case–control	$N = 215$ (107 ASD cases and 108 controls)	14 participants with missing data were excluded	ASD cases identifed from clinical records, four local pediatricians, and recruitment posters; controls from recruitment posters, matched by sex and age	Maternal self-reports at the time of the study (after ASD diagnosis), when children were 0–10 years of age	ASD diagnoses at < 6 years of age, reported by mother

Table 3 Characteristics of studies on prenatal acetaminophen use and other neurodevelopmental disorders (NDDs)

Authors, Year	Location	Study Period	Risk Estimate	Study Design	Sample Size	Missing Data	Inclusion Criteria	Exposure Definition	Outcome Definition
Bertoldi, 2020	USA—Brazil	1999 and 2002, Project Viva; Pelotas 2015	Project Viva: Exposure to acetaminophen in both 1st and 2nd trimester of pregnancy and early childhood cognitive outcomes: Wide Range Achievement of Visual Motor Abilities (WRAVMA)—drawing: β = −1.53 (95% CI: −2.93, −0.13) Exposure to acetaminophen during pregnancy: WRAVMA—drawing: β = −0.63 (95% CI: −1.20, −0.06) Pelotas cohort: Exposure to acetaminophen in both 1st and 2nd trimester of pregnancy and early childhood cognitive outcomes: INTERGROWTH-21st Neurodevelopment Assessment (INTER-NDA): Total: β = 0.09 (95% CI: 0.02–0.16)	Cohorts	Project Viva: *N* = 1,217 Pelotas: *N* = 3,818	To address the issue of missing outcome data, they implemented inverse probability weighting; they did not use multiple imputation because most covariates had < 5% missing values	Project Viva: Single pregnancies, who had intention to remain in the geographical area, were fluent in English, and presented by the 22nd week of gestation Pelotas: Gave birth in any of five maternity hospitals of the city in 1 January–31 December 2015 and lived in the urban area	Project Viva: Mothers were asked to categorize their acetaminophen use during this pregnancy for the early pregnancy interview and in the past 3 months for the mid-pregnancy interview Pelotas: Women were asked about any medication use during pregnancy at prenatal and perinatal interviews	Project Viva: Children's cognition using the Peabody Picture Vocabulary Test (PPVT-III) and the Wide Range Achievement of Visual Motor Abilities (WRAVMA) Pelotas: Children's cognitive development at a 24-month follow-up visit was evaluated using the INTERGROWTH-21st Neurodevelopment Assessment (INTER-NDA)

Table 3 (continued)

Authors, Year	Location	Study Period	Risk Estimate	Study Design	Sample Size	Missing Data	Inclusion Criteria	Exposure Definition	Outcome Definition
Bornehag, 2018	Switzerland	2007–2010	Odds ratio (OR) for language delays among girls whose mothers reported > 6 vs. 0 acetaminophen tablets during pregnancy: OR = 5.92 (95% CI: 1.10–31.94) OR for LD in girls whose mothers' urinary APAP was in the highest compared to the lowest quartile: OR = 10.34 (95% CI: 1.37–77.86)	Cohort	*N* = 754	NA	Pregnant women who could read Swedish and were not planning to move out of the country	Two exposure measures were used: (1) maternally reported number of acetaminophen tablets taken between conception and enrollment; (2) acetaminophen urinary concentration at enrollment	Nurse evaluation and parental questionnaire on language use at 30 months of age
Brandlistuen, 2013 (overall study)	Norway	1999–2008	Prenatal paracetamol for > 28 days: Poorer gross motor development: β = 0.05 (95% CI: 0.002–0.11) Poor communication: β = 0.08 (95% CI: 0.02–0.14) Poor externalizing behaviour: β = 0.13 (95% CI: 0.07–0.18) Poor internalizing behaviour: β = 0.03 (95% CI:–0.03–0.08) Higher activity levels: β = 0.001 (95% CI: –0.05–0.04) Short- term use of paracetamol (1–27 days): Poor gross motor outcomes: β = 0.03 (95% CI: 0.01– 0.05)	Prospective cohort	26,613	Multiple imputation	NA	Information on paracetamol use was obtained from two prenatal questionnaires; groups were divided in short-term (1–28 days of use) and long-term (≥ 28 days)	Psychomotor development: Norwegian version of the Ages and Stages Questionnaire (ASQ) Externalizing and internalizing behaviours: Child Behaviour Checklist (CBCL/ 1 1/2–5/ LDS) Temperament: Emotionality, Activity and Shyness Temperament Questionnaire (EAS)

Table 3 (continued)

Authors, Year	Location	Study Period	Risk Estimate	Study Design	Sample Size	Missing Data	Inclusion Criteria	Exposure Definition	Outcome Definition
Brandlistuen, 2013 (sibling control study)	Norway	1999–2008	Prenatal paracetamol for > 28 days: Poorer gross motor development: β = 0.24 (95% CI: 0.12–0.51) Poor communication: β = 0.20 (95% CI: 0.01–0.39) Poor externalizing behaviour: β = 0.28 (95% CI: 0.15–0.42) Poor internalizing behaviour: β = 0.14 (95% CI: 0.01– 0.28) Higher activity levels: β = 0.24 (95% CI: 0.11–0.38) Short- term use of paracetamol (1–27 days): Poor gross motor outcomes: β = 0.10 (95% CI: 0.02– 0.19)	Prospective cohort	*N* = 2,919 same-sex sibling pairs	Multiple imputation	NA	Information on paracetamol use was obtained from two prenatal questionnaires; groups were divided in short-term (1–28 days of use) and long-term (≥ 28 days)	Psychomotor development: Norwegian version of the Ages and Stages Questionnaire (ASQ) Externalizing and internalizing behaviours: Child Behaviour Checklist (CBCL/ 11/2–5/ LDS) Temperament: Emotionality, Activity and Shyness Temperament Questionnaire (EAS)

Table 3 (continued)

Authors, Year	Location	Study Period	Risk Estimate	Study Design	Sample Size	Missing Data	Inclusion Criteria	Exposure Definition	Outcome Definition
Golding, 2019	UK	1991–1992	Mean differences in cognition and behaviour measures and paracetamol exposure at 18–32 weeks gestation: IQ—Freedom from distractibility at 8 years: Adjusted mean difference (AMD) = −0.35 (95% CI: −0.69, −0.00) M.SDQ Hyperactivity at 42 months: AMD = 0.16 (95% CI: 0.07–0.25) M.SDQ Hyperactivity at 47 months: AMD = 0.22 (95% CI: 0.10–0.33) Development and Well-being Assessment (T.DAWBA) Attention at 7–8 years: AMD = 0.45 (95% CI: 0.11–0.79) T.DAWBA Attention/ Activity at 7–8 years: AMD = 0.53 (95% CI: 0.02–1.04)	Cohort	*N* = 12,418	NA	Pregnant women who were residents in Avon, UK, with at least one questionnaire returned and no misscarriage	Questionnaire at ~ 32 weeks gestation	Strengths and Difficulties Questionnaire (SDQ); 18 measures of cognitive function considered, 11 relating to IQ (not clear what test they used); 11 measures of the child's temperament (not clear)

Table 3 (continued)

Authors, Year	Location	Study Period	Risk Estimate	Study Design	Sample Size	Missing Data	Inclusion Criteria	Exposure Definition	Outcome Definition
Inoue, 2021	Denmark	23	Risk ratios (RR) for behavioral difficulties at age 11 years: Parent reported: Strengths and Difficulties Questionnaire (SDQ)—composite score: RR = 1.14 (95% CI: 1.01–1.29) Internalizing: RR = 1.09 (95% CI: 1.00–1.19) SDQ—Emotional symptoms: RR = 1.16 (95% CI: 1.09–1.24) Hyperactivity: RR = 1.12 (1.02–1.24) Child-reported: Strengths and Difficulties Questionnaire (SDQ)—composite score: RR = 1.40 (95% CI: 1.20–1.63) Internalizing: RR = 1.13 (95% CI: 1.04–1.23) Externalizing: RR = 1.13 (95% CI: 1.05–1.22) SDQ—Emotional symptoms: RR = 1.17 (95% CI: 1.02–1.34) Hyperactivity: RR = 1.18 (1.08–1.29)	Cohort	*N* = 40,934	Multiple imputation (10 simulated complete datasets were generated assuming multivariate normal distribution for about 8% of participants who had at least 1 missing covariate value)	Mothers, with live-born children, who answered the study enrollment form and three subsequent telephone interviews (12th and 30th gestational weeks and at 6 months after birth)	Information about acetaminophen exposure was obtained from the study enrollment form and three computer-assisted telephone interviews	Children's behaviors were assessed based on the standardized Strengths and Difficulties Questionnaire (SDQ)

Table 3 (continued)

Authors, Year	Location	Study Period	Risk Estimate	Study Design	Sample Size	Missing Data	Inclusion Criteria	Exposure Definition	Outcome Definition
Laue, 2019	Canada	2007–2009	Estimates for the association between prepregnancy acetaminophen exposure and neurocognitive development: Coding: Low exposure: 1.03 (95% CI: −0.22–2.29) High exposure: 0.74 (95% CI: −0.54–2.01) Block Design subtest: Low exposure: 1.03 (95% CI: −0.22–2.29) High exposure: −0.92 (95% CI: −2.20–0.37)	Cohort	*N* = 118	Excluded	Pregnant women living in Sherbrooke, Quebec, Canada recruited in 2007–2009 during the first trimester of pregnancy and at delivery	Acetaminophen was extracted from < 120 mg meconium by solid–liquid extraction in ethyl acetate followed by purification with a dispersive solid phase extraction in acetonitrile	Neurocognitive development was evaluated using the Wechsler Intelligence Scale for Children, 4th edition (WISC-IV)
Liew, 2016	Denmark	1996–2002	Prenatal acetaminophen and IQ: Mean difference in full-scale IQ in 1–5 weeks of use: −3.1 (95% CI: −5.6,−0.68) Mean difference in performance IQ in 1–5 weeks of use: −4.1 (95% CI: −7.3, −0.88)	Cohort	*N* = 1,491	Multiple imputation	Sampling was based on maternal alcohol and binge drinking reported during pregnancy with an oversampling strategy; women who spoke insufficient Danish or did not intend to complete their pregnancy were excluded	Information about acetaminophen use was collected in three telephone interviews conducted at gestational weeks 12 and 30	Child IQ was assessed using the Wechsler Primary and Preschool Scales of intelligence-revised (WPPSi-r); the cohort used a shorter version that includes three verbal and three performance sub-tests designed to shorten test duration

Table 3 (continued)

Authors, Year	Location	Study Period	Risk Estimate	Study Design	Sample Size	Missing Data	Inclusion Criteria	Exposure Definition	Outcome Definition
Parker, 2020	USA and Canada	1996–2002	Any use of acetaminophen was associated with mother-reported behavioral problems (mean differences [MD] = 2.2 [95% CI: 0.3–4.1]) MD was similar for both internalizing (MD = 2.5 [95% CI: 0.8–4.3]) and externalizing (MD = 1.9 [95% CI: 0.1–3.7]) broadband scales	Cohort	*N* = 560	NA	Data on maternal exposures during pregnancy and at least one neurodevelopmental assessment in childhood	Standardized interview administered after delivery and prior to childhood neurodevelopmental assessments	The Child Behavior Checklist (CBCL) and Teacher-Report Form (TRF), tests that are part of the Achenbach System of Empirically Based Assessment (ASEBA), were used to assess common child behavior problems

Table 3 (continued)

Authors, Year	Location	Study Period	Risk Estimate	Study Design	Sample Size	Missing Data	Inclusion Criteria	Exposure Definition	Outcome Definition
Rifas-Shiman, 2020	USA	1999–2002	Behaviour Rating Inventory of Executive Function (BRIEF) Global Executive Composite: β = 1.64 (95% CI: 0.59–2.68) Behaviour Regulation Index: β = 1.45 (95% CI: 0.44–2.47) BRIEF Metacognition Index: β = 1.29 (95% CI: 0.29–2.30) Infancy exposure (≥ 6 versus < 6 times) to acetaminophen and higher parent-rated BRIEF—Global Executive Composite score (GEC) scores: BRIEF—Global Executive Composite: β = 1.69 (95% CI: 0.51–2.87) Behaviour Regulation Index: β = 1.26 (95% CI: 0.08–2.45) BRIEF Metacognition Index: β = 1.67 (95% CI: 0.54–2.81) Strengths and Difficulties Questionnaire (SDQ) Total Difficulties: β = 1.19 (95% CI: 0.58–1.80)	Cohort	*N* = 1,225	Multiple imputation	Women with single pregnancies, who had intention to remain in the geographical area, were fluent in English, and presented by the 22nd week of gestation	Mothers were asked to categorize their acetaminophen use during this pregnancy for the early pregnancy interview (1st trimester) and in the past 3 months for the mid-pregnancy interview (2nd trimester)	Behavoiur Rating Inventory of Executive Function (BRIEF) and the Strengths and Difficulties Questionnaire (SDQ)

Table 3 (continued)

Authors, Year	Location	Study Period	Risk Estimate	Study Design	Sample Size	Missing Data	Inclusion Criteria	Exposure Definition	Outcome Definition
Ruisch, 2018	UK	1991–1992	Paracetamol exposure during pregnancy and oppositional-defiant disorder (ODD) and conduct disorder (CD) symptoms: ODD scores—Teacher rated: Incidence rate ratio (IRR) = 1.21 (95% CI: 1.06–1.38) CD symptom scores—Maternal rated: IRR = 1.14 (95% CI: 1.05–1.24) CD symtom scores—Teacher rated: IRR = 1.25 (95% CI: 1.01–1.53)	Cohort	*N*≈6,300 for maternal and *N*≈4,400 for teacher ratings	NA	Pregnant women who were residents in Avon, UK, with at least one questionnaire returned and no misscarriage	Questionnaires at 18 weeks gestation	Development and Well-Being Assessment (DAWBA)
Skovlund, 2017	Norway	1999–2008	Odds ratios of having a child with lower communication skills according to use of paracetamol: Two periods (trimesters): adjusted OR = 1.09 (95% CI: 1.04–1.15) Three periods (trimesters): Adjusted OR = 1.17 (95% CI: 1.06–1.30)	Cohort	*N* = 58,410	Excluded	Pregnant women in Norway who agreed to participate prior to first ultrasound scan at weeks 17–18	Mothers were asked to report on medication use at pregnancy weeks 17–18 and 30	Language competence at 3 years of age was evaluated by a validated language grammar rating scale (Dale, 2003; PMID: 14,696,985)
Streissguth, 1987	Seattle, USA	1974–1975	IQ scores on aspirin and acetaminophen: Linear model: β(SE) = 0.28 (0.54); p = 0.61 Binary model: β(SE) = 0.37 (0.54); p = 0.49	Cohort	*N* = 421	NA	A consecutive group of pregnant women receiving prenatal care in 1974–1975, interviewed during the 5th month of pregnancy in their own homes	Self-report at 5 months gestation	Child IQ assessed with the Weschler Preschool and Primary Scale of Intelligence (WPPSD)

Table 3 (continued)

Authors, Year	Location	Study Period	Risk Estimate	Study Design	Sample Size	Missing Data	Inclusion Criteria	Exposure Definition	Outcome Definition
Tovo-Rodrigues, 2020	Brazil	2004	Acetaminophen during pregnancy and neurodevelopmental performance: Low performance in BDI: RR = 1.00 (95% CI: 0.78–1.28) Social-personal area: RR = 1.00 (95% CI: 0.80–1.25) Adaptative area: RR = 0.91 (95% CI: 0.76–1.08) Motor area: RR = 0.91 (95% CI: 0.71–1.16) Communication area: RR = 1.04 (95% CI: 0.84–1.30) Cognitive area: RR = 0.92 (95% CI: 0.83–1.02)	Cohort	*N* = 3,737	Missing data were handled using inverse probability weighting	Mothers were those living in the urban area of Pelotas or in Jardim América	Standardised questionnaire applied at the perinatal evaluation; use of acetaminophen was defined as at least once during pregnancy, regardless of the dose used	The screening version of Battelle's Developmental Inventory (BDI) was used to assess children development at 24 months of age Child behavioral/emotional problems were assessed at 48 months using the Child Behaviour Checklist (CBCL)
Tronnes, 2020	Norway	1999–2008	Paracetamol exposure during pregnancy and behavioral problems in preschool-age: Paracetamol use in three trimesters: adjusted RR = 1.36 (95% CI: 1.02–1.80) Paracetamol exposure during pregnancy and temperamental traits: Paracetamol use in two trimesters—Shyness: adjusted RR = −0.62 (95% CI: − 1.05, − 0.19)	Cohort	*N* = 32,934	NA (not even in supplementary material)	Pregnant women at their routine ultrasound examination at gestational week 17–18	Information about medication use was obtained from two prenatal questionnaires	Communication skills were assessed by the Ages and Stages Questionnaire (ASQ) Selected items from the Child Behaviour Checklist (CBCL) for preschool children (CBCL/ 1.5–5) were used to assess children's behavior Temperament was assessed by the short version of the Emotionality, Activity and Shyness Temperament Questionnaire (EAS)

Table 3 (continued)

Authors, Year	Location	Study Period	Risk Estimate	Study Design	Sample Size	Missing Data	Inclusion Criteria	Exposure Definition	Outcome Definition
Vlenterie, 2016	Norway	1999–2008	Paracetamol exposure and psychomotor and behavioural outcomes in 18-month-old infants: Psychomotor problems: Fine motor: OR = 1.17 (95% CI: 1.01–1.36) Delayed motor milestone attainment: OR = 1.35 (95% CI: 1.07–1.70) Communication: OR = 1.32 (95% CI: 1.05–1.66) Behavioural problems: Externalizing: OR = 1.50 (95% CI: 1.26–1.76)	Cohort	*N* = 51,200	NA	Pregnant women at their routine ultrasound examination at gestational week 17–18	Information about medication use was obtained from two prenatal questionnaires	
Woodbury, 2024	Illinois, USA	Pregnancies:2013–2020	Vocabulary (CDI) β = −0.58 (95% CI −1.13, −0.04) 2nd Trimester, β = −1.83 (−3.13, −0.54) 3rd trimester. Mean length of utterance(CDI) β = −0.01 (−0.01, 0.001) 2nd trimester, B = −0.02 (−0.04,−0.003) 3rd trimester	Prospective cohort	*N* = 532	Exclusion	18–40 year old English speaking pregnant women invited at 1st prenatal visit, not yet 15 weeks gestation, no other children in cohort, resided nearby, carrying singleton, considered low risk, plan to remain in area until child's 1st birthday	Maternal interview at 6 time points. 5 during pregnancy and 1 at birth	Early language development evaluated using the MacArthur-Bates Communicative Development Inventories: Words and Sentences (CDI) and the Speech and Language Assessment Scale (SLAS)

Table 3 (continued)

Authors, Year	Location	Study Period	Risk Estimate	Study Design	Sample Size	Missing Data	Inclusion Criteria	Exposure Definition	Outcome Definition
Zhou, 2024	Beijing, China	2018–2024	No risk estimate provided but stated APAP was associated with gross motor. Mean SHAP value for Gross Motor 0.073 (interpretable machine language method calculate SHapley Additive exPlanations (SHAP) to explain variable contribution in the predictive model)	Prospective cohort	*N* = 1125	Exclusion also interpolated maternal missing data using either the multitude or median and for offspring interpolated using the mean of the other area scores for that individual	Singleton, live births with data regarding maternal medication usage and completion of ASQ-3 questionnaire in 1st year	In-patient and out-patient prescription data prescribed from the start of last menstrual period until delivery	Parent administered, Chinese Ages and Stages Questionnaire-3 (ASQ-3) assessing communication, gross motor, fine motor, problem solving & person-social in first year

studies ($n=19$), where exposure was recorded in real time, and retrospective or historical cohort studies ($n=15$), where data were collected retrospectively or from existing cohorts, this distinction was considered in the risk-of-bias assessment; case–control studies ($n=2$), and three sibling-controlled cohort studies ($n=3$). Sample sizes ranged from $N=118$ participants to $N=105{,}208$ participants.

Quality assessment

Most of the reviewed studies showed robust study designs and methods, large sample sizes (> 500 participants) [52], and controlled for potential sources of bias and confounding. Those considered as low quality [36] were not included in the systematic review. To enhance transparency, Tables 4–9 provide detailed risk-of-bias (Tables 4, 6, 8), strength-of-evidence, and expert opinion scores for the 46 studies. Risk-of-bias ratings, based on domains like confounding and exposure, averaged 0.33–0.85 (e.g., ADHD: 0.85). High-scoring examples include Bornehag et al. [47], with a score of 0.63 due to strong confounder control, while Ahlqvist et al. [33] scored 0.85 due to exposure limitations. Strength-of-evidence (e.g., 0.75) and expert scores varied, with Baker et al. [17] at 1.17 for dose–response, versus Ahlqvist et al. at 0 for small effects, reflecting design and analytical rigor.

The 46 studies were evaluated for their associations with neurodevelopmental disorders. For ADHD, among the 20 studies, 14 reported positive associations, 3 showed null associations, 1 indicated an inverse association, and 2 had mixed results. For ASD, among the 8 studies, 5 reported positive associations, 2 showed null associations, and 1 had mixed results. For other NDDs, among the 18 studies, 6 reported positive associations, 4 indicated inverse associations, 2 showed null associations, and 6 had mixed results. These categories, derived from the Navigation Guide's strength-of-evidence framework, highlight the variability in findings and mitigate confirmation bias by including all outcome types.

ADHD

We evaluated the quality of 20 studies of the association between prenatal acetaminophen use and risk of ADHD in children and rated each study in terms of bias (Table 4) and strength of evidence (Table 5). The average bias score was 0.85; the average strength of evidence was rated as 0.75 the average expert opinion score was 0.70. The reviewed studies consistently reported a positive association between prenatal acetaminophen use and ADHD, with an exposure–response (dose–response) relationship observed in several studies. Most studies rated at lower quality received those scores because of limitations likely to bias their results toward the null. Therefore, those studies likely underestimate associations between prenatal acetaminophen and ADHD. Ultimately, the obtained scores suggest strong evidence of a likely relationship between prenatal acetaminophen use and increased risk of ADHD in children, including high-quality studies that provide very strong evidence of an association and studies that provide strong evidence of an association (Fig. 2).

ASD

We evaluated the quality of six studies on the association between prenatal acetaminophen use and the risk of ASD in children. We rated each study in terms of bias (Table 6) and strength of evidence (Table 7). The average bias score was 0.33, the average strength of evidence was rated as 1.17, and the average expert opinion score was 0.50. The reviewed studies consistently reported a positive association between prenatal acetaminophen use and ASD, with an exposure–response relationship observed in four of the five studies that evaluated the relationship. Ultimately, there was strong evidence of a relationship between prenatal acetaminophen use and increased risk of ASD in children (Fig. 2).

Other NDDs

We evaluated the quality of 18 studies of the association between prenatal acetaminophen use and risk of other NDDs in children and rated each study in terms of bias (Table 8) and strength of evidence (Table 9). The average bias score was 0.63; the average strength of evidence was rated as 1.19; the average expert opinion score was 1.38. Many studies consistently reported a positive association between prenatal acetaminophen use and other NDDs, with an exposure–response relationship observed in some studies. Ultimately, there was strong evidence of an association between prenatal acetaminophen use and increased risk of other NDDs in children, including nine high-quality studies[53] that provided very strong evidence of an association (Fig. 2).

Assessment of residual confounding

Taken as a whole, the reviewed epidemiology studies controlled for measurable confounders and attempted to account for the possibility of unmeasurable or residual confounding. To address the possibility of confounding, studies controlled for factors that might influence acetaminophen use directly or indirectly and also are known risk factors for NDDs, including: maternal age, maternal illness, maternal use of medications other than acetaminophen, maternal intelligence, parental education levels, socioeconomic status, maternal drinking, maternal smoking, maternal drug use, genetic confounding, confounding due to indication (i.e., clinical reason for taking the medication), and other risk factors for NDDs

Table 4 Rating of bias of studies on prenatal acetaminophen use and attention-deficit/hyperactivity disorder (ADHD)

Author	1. Selection	2. Blinding	3. Exposure	4. Outcomes	5. Confounding	6. Incomplete Data Addressed	7. Selecting Outcome	8. Financial Interest	9. Risk of Bias
Ahlqvist, 2024 (overall study)	1	1	3	1	1	1	1	1	2
Ahlqvist, 2024 (sibling-controlled study)	1	1	4	1	3	1	1	1	3
Alemany, 2021	1	1	2	1	1	1	1	1	1
Avella-Garcia, 2016	1	1	2	2	1	1	1	1	1
Baker, 2020	1	1	1	1	1	1	1	1	1
Baker, 2025	1	1	1	2	2	1	1	1	1
Chen, 2019	1	1	1	1	1	1	1	1	1
Gustavson, 2021 (overall study)	1	1	2	1	1	2	1	2	1
Gustavson, 2021 (sibling-controlled study)	1	1	2	1	3	2	1	2	1
Ji, 2020	1	1	1	1	1	1	1	1	1
Liew, 2014	1	1	2	1	1	1	1	1	1
Liew, 2016	1	1	2	1	1	1	1	1	1
Liew, 2019	1	1	2	1	1	2	1	1	1
Stergiakouli, 2016	1	1	2	2	1	1	1	1	1
Streissguth, 1987	1	1	2	3	2	1	1	1	1
Sznajder, 2022	1	1	2	2	2	1	1	1	1
Thompson, 2014	1	1	2	2	1	2	1	1	1
Tovo-Rodrigues, 2018	1	1	3	2	2	2	1	1	1
Woodbury, 2024	1	1	1	2	1	1	1	1	1
Ystrom 2017	1	1	2	1	1	1	1	1	1

1. Was the strategy for recruiting participants consistent across study groups?

2. Was knowledge of the group assignments inadequately prevented (i.e., blinded or masked) during the study, potentially leading to subjective measurement of either exposure or outcome?

3. Were exposure assessment methods lacking accuracy?

4. Were outcome assessment methods lacking accuracy?

5. Was potential confounding inadequately incorporated?

6. Were incomplete outcome data inadequately addressed?

7. Does the study appear to have selective outcome reporting?

8. Did the study receive any support from a company, study author, or other entity having a financial interest in any of the exposures studied?

9. Did the study appear to have other problems that could put it at a risk of bias?

Scoring: 1 – low risk of bias; 2 – probably low risk of bias; 3 – probably high risk of bias; 4 – high risk of bias

including child birth weight, child gestational age as well as some others. Some studies also included negative control exposure periods (e.g., comparison between acetaminophen use before/after vs. during pregnancy, comparing associations with the use of other pain reliever medications) to determine whether unmeasured and residual sources of confounding might drive the associations. Some of these studies included other strengths, such as valid exposure assessment methods (i.e., detection of acetaminophen in meconium, cord blood, maternal plasma and maternal urine), blinding of mother to disease outcome in prospective designs, high-quality outcome measures, as well as differences in population type and country, with some prospective studies finding dose–response. The associations persisted after controlling for those confounders and risk factors — a child exposed to acetaminophen in utero still had a higher risk of developing neurodevelopmental symptoms and/or being diagnosed with NDDs than a child who was not exposed. These adjusted results provide strong evidence that the observed relationship was not confounded but in fact was likely relationship, even though there is, as always, a possibility for residual confounding.

Table 5 Study grading of studies on prenatal acetaminophen use and attention-deficit/hyperactivity disorder (ADHD)

Author, Year	a. Size	b. Large Effect (> 2)	c. Dose Response	d. Internal Consistency	e. Control of Bias	f. Other	Average of Criteria	Sum of Criteria	Strength of Evidence	Expert Opinion Score
Baker, 2025	−1	2	0	2	2	2	1.17	7	2	2
Ahlqvist, 2024 (overall study)	2	−1	2	2	−1	NA	0.8	4	1	−1
Ahlqvist, 2024 (sibling -controlled study)	2	−2	0	2	−2	NA	0	0	−1	−2
Woodbury, 2024	−1	0	2	2	1	NA	0.8	4	1	1
Ystrom, 2017	2	1	2	2	1	NA	1.6	8	1	2
Sznajder, 2022	1	0	0	0	1	NA	0.4	2	0	0
Baker, 2020	−1	2	2	2	2	2	1.5	9	2	2
Alemany, 2021	2	0	0	1	1	NA	1	5	1	1
Gustavson, 2021 (overall study)	2	2	0	1	2	−1	1	6	1	2
Gustavson, 2021 (sibling-controlled study)	−1	−1	0	2	1	−1	−0.3	−2	0	−1
Ji, 2020	0	2	2	1	2	2	1.5	9	2	2
Chen, 2019	1	0	0	2	2	NA	0.6	3	1	1
Liew, 2019	2	0	0	2	1	NA	0.6	3	1	2
Tovo-Rodrigues, 2018	1	0	0	1	1	NA	0	0	0	0
Liew, 2016	1	1	2	2	0	NA	1.6	8	2	2
Avella-Garcia, 2016	1	0	2	2	1	NA	1.4	7	0	0
Stergiakouli, 2016	2	0	0	2	1	NA	1	5	1	1
Thompson, 2014	0	−1	0	1	1	NA	0.2	1	0	0
Liew, 2014	2	0	2	2	0	NA	1.2	6	1	1
Streissguth, 1987	−1	−1	0	−1	0	NA	−0.6	−3	−1	−1
Score study of evidence: 2 – very strong; 1 – strong; 0 – moderate; -1 – weak; -2 – very weak/none										
Average score	0.8	0.2	0.8	1.50	0.85	0.8	0.77	4.1	0.75	0.7
Average before add'l studies	0.8	0.27	0.67	1.33	1.07	0.50	0.74	3.93	0.73	0.80

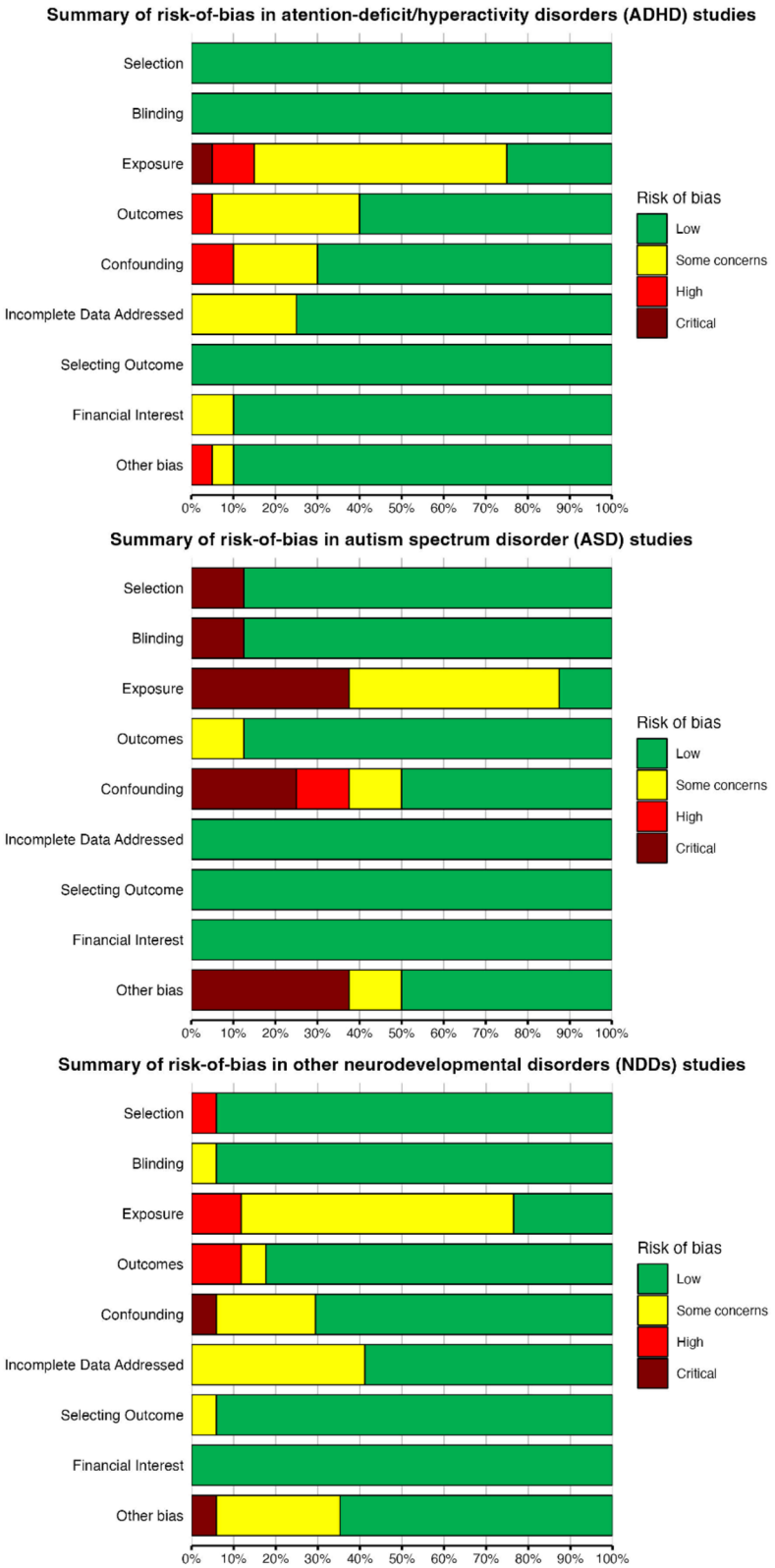

Fig. 2 Risk-of-bias per outcome in the current Navigation Guide analyses

Table 6 Rating of bias of studies on prenatal acetaminophen use and autism spectrum disorder (ASD)

Author	1. Selection	2. Blinding	3. Exposure	4. Outcomes	5. Confounding	6. Incomplete Data Addressed	7. Selecting Outcome	8. Financial Interest	9. Risk of Bias
Ahlqvist, 2024 (overall study)	1	1	4	1	1	1	1	1	2
Ahlqvist, 2024 (sibling control study)	1	1	4	1	3	1	1	1	4
Alemany, 2021	1	1	2	1	2	1	1	1	1
Avella-Garcia, 2016	1	1	2	1	1	1	1	1	1
Ji, 2020	1	1	1	1	1	1	1	1	1
Leppert, 2019	1	1	2	1	4	1	1	1	4
Liew, 2016	1	1	2	1	1	1	1	1	1
Saunders, 2019	4	4	4	2	4	1	1	1	4

1. Was the strategy for recruiting participants consistent across study groups?

2. Was knowledge of the group assignments inadequately prevented (i.e., blinded or masked) during the study, potentially leading to subjective measurement of either exposure or outcome?

3. Were exposure assessment methods lacking accuracy?

4. Were outcome assessment methods lacking accuracy?

5. Was potential confounding inadequately incorporated?

6. Were incomplete outcome data inadequately addressed?

7. Does the study appear to have selective outcome reporting?

8. Did the study receive any support from a company, study author, or other entity having a financial interest in any of the exposures studied?

9. Did the study appear to have other problems that could put it at a risk of bias?

Scoring: 1 – low risk of bias; 2 – probably low risk of bias; 3 – probably high risk of bias; 4 – high risk of bias

Discussion

Our Navigation Guide-based evaluation of the existing literature showed a strong, consistent association between prenatal acetaminophen exposure and ADHD/ASD/other NDDs. These studies were controlled for multiple potential confounders that might have plausibly explained the associations, yet the associations persisted. After directly controlling for confounders or employing sophisticated study designs such as using negative control exposure periods (e.g., comparing acetaminophen use before/after vs. during pregnancy, comparing associations with the use of other pain relievers), and/or propensity score matching to determine whether unmeasured and residual sources of confounding might drive these associations, the associations persisted. While studies used different scales to assess ADHD in the offspring, and some of them relied on parental reports only, this pattern reflects real-life research—similar to the literature of epidemiological studies on other established risk factor of disease. The majority of the studies show consistency between their results. Most results are consistent across different time periods, datasets, and patient populations: when a mother takes acetaminophen while pregnant, the odds of her child having an NDD, including ADHD or ASD, increased, and these associations were also formally statistically significant. During data extraction and quality assessment, we collected data on the timing of acetaminophen exposure during gestation, including whether it occurred in the first, second, or third trimester, or across the full pregnancy, using maternal self-reports, biomarkers (e.g., meconium, cord blood), or medical records. A subset of the studies stratified results by trimester or specific gestational weeks (e.g., [27]), and we evaluated these to identify potential windows of heightened vulnerability. Although not all studies provided granular timing data, those that did showed stronger associations with exposure in the second and third trimesters. Timing, dosage, and duration were integrated into the strength and consistency of evidence assessment, which may be helpful to inform clinical implications.

Although acetaminophen remains the preferred analgesic due to its relatively favorable safety profile compared to other medications, its use should be approached judiciously, particularly in light of potential implications for fetal development during perinatal period[54]. Given acetaminophen's role as the first-line analgesic and antipyretic during pregnancy, due to the known harms of NSAIDs, our findings must be contextualized clinically. NSAIDs may pose teratogenic risks, particularly in the third trimester[55] leaving no clear pharmacological alternative. For fever management, non-pharmacologic options (e.g., physical cooling) or medical consultation are recommended[57]. We advocate

Table 7 Study grading of studies on prenatal acetaminophen use and autism spectrum disorder (ASD)

Author, Year	a. Size	b. Large Effect (>2)	c. Dose Response	d. Internal Consistency	e. Control of Bias	f. Other	Average of Criteria	Sum of Criteria	Strength of Evidence	Expert Opinion Score
Ahlqvist, 2024 (overall study)	2	−1	2	2	−1	NA	0.8	4	1	−1
Ahlqvist, 2024 (sibling control study)	2	−2	0	2	−2	NA	0	0	0	−2
Alemany, 2021	2	0	0	2	1	NA	1	5	1	1
Avella-Garcia, 2016	1	0	0	2	1	NA	0.8	4	1	1
Ji, 2020	0	2	2	2	2	NA	1.6	8	2	2
Liew, 2016	2	1	2	2	1	NA	1.6	8	2	2
Score study of evidence: +2 – very strong; +1 – strong; 0 – moderate; -1 – weak; -2 – very weak/none										
Average	1.50	0.00	1.00	2.00	0.33	NA	0.97	4.83	1.17	0.50
Before ahlqvist	1.25	0.75	1	2	1.25	na	1.25	6.25	1.5	1.5

Table 8 Rating of bias of studies on prenatal acetaminophen use and other neurodevelopmental disorders

Author	1. Selection	2. Blinding	3. Exposure	4. Outcomes	5. Confounding	6. Incomplete Data Addressed	7. Selecting Outcome	8. Financial Interest	9. Risk of Bias
Bertoldi, 2020	1	1	2	1	1	1	1	1	1
Bornehag, 2018	1	1	1	1	2	2	1	1	2
Brandlistuen, 2013	1	1	2	1	1	1	1	1	1
Golding, 2019	1	1	2	1	2	2	1	1	2
Inoue, 2021	1	1	2	1	1	1	1	1	1
Laue, 2019	1	1	1	1	1	1	1	1	2
Liew, 2016	1	1	2	1	1	1	1	1	1
Parker, 2020	3	2	3	2	1	2	1	1	1
Rifas-Shiman, 2020	1	1	2	1	1	1	1	1	1
Ruisch, 2018	1	1	2	1	2	2	1	1	2
Skovlund, 2017	1	1	1	3	1	1	1	1	1
Streissguth, 1987	1	1	2	1	1	2	1	1	1
Tovo-Rodrigues, 2020	1	1	3	1	1	1	1	1	1
Tronnes, 2020	1	1	2	1	1	2	1	1	1
Vlenterie, 2016	1	1	2	1	1	2	1	1	1
Woodbury-2, 2024	1	1	1	1	2	1	2	1	2
Zhou, 2024	1	1	2	3	4	1	1	1	4

1. Was the strategy for recruiting participants consistent across study groups?

2. Was knowledge of the group assignments inadequately prevented (i.e., blinded or masked) during the study, potentially leading to subjective measurement of either exposure or outcome?

3. Were exposure assessment methods lacking accuracy?

4. Were outcome assessment methods lacking accuracy?

5. Was potential confounding inadequately incorporated?

6. Were incomplete outcome data inadequately addressed?

7. Does the study appear to have selective outcome reporting?

8. Did the study receive any support from a company, study author, or other entity having a financial interest in any of the exposures studied?

9. Did the study appear to have other problems that could put it at a risk of bias?

Scoring: 1 – low risk of bias; 2 – probably low risk of bias; 3 – probably high risk of bias; 4 – high risk of bias

cautious, time-limited acetaminophen use under medical guidance, highlighting the need for research into safer alternatives and updated guidelines.

The literature includes three sibling-controlled studies, which require special consideration. Sibling control designs have been proposed in the attempt of using within-pair comparison to control confounding from shared familial factors such as socioeconomic or genetic factors[53]. In one of these studies, Gustavson et al. ran a careful, detailed evaluation of the role of prenatal exposure to acetaminophen on ADHD, including a sibling analysis [58]. This study carried out extensive bias analyses and showed that the entire effect disappeared in the sibling-controlled analyses. Bias analyses are crucial in epidemiological research, especially in observational studies, to ensure the validity and reliability of findings [59]. By identifying and adjusting for biases such as confounding, selection bias, and information bias, epidemiologists accurately estimate the genuine relationship between exposures and outcomes [60]. However, sibling comparison analyses have significant limitations that affect their interpretation. Only sibling pairs discordant on both exposure and outcome contribute to "within-pair" association, leading to strongly reduced statistical power compared to full cohort analyses. Specifically, the study by Gustavson et al. had a small sample size for investigating long term acetaminophen exposure ($N=34$ discordant pairs).

Previous systematic reviews and meta-analyses have explored the link between acetaminophen and ASD, ADHD, and NDD. For example, Masarwa et al. (2018) conducted a systematic review, meta-analysis, and meta-regression of cohort studies to investigate the association between prenatal acetaminophen exposure and the risk of attention deficit hyperactivity disorder (ADHD) and autistic spectrum disorder (ASD). They used the Newcastle–Ottawa Scale (NOS)[13] tool for assessing the quality of nonrandomized studies. Their findings indicate that prenatal exposure to acetaminophen is associated with an increased risk of both

Table 9 Study grading of studies on prenatal acetaminophen use and other neurodevelopmental disorders

Author, Year	a. Size	b. Large Effect (> 2)	c. Dose Response	d. Internal Consistency	e. Control of Bias	f. Other	Average of Criteria	Sum of Criteria	Strength of Evidence	Expert Opinion Score
Bertoldi, 2020	1	0	0	2	0	1	0.67	4	1	1
Bornehag, 2018	0	2	0	0	−1	1	0.33	2	1	1
Brandlistuen, 2013	1	1	0	2	1	1	1.00	6	2	2
Golding, 2019	2	0	0	2	0	1	0.83	5	1	2
Inoue, 2021	2	0	1	2	1	1	1.17	7	2	2
Laue, 2019	−2	−1	0	0	2	2	0.17	1	0	1
Liew, 2016	1	1	0	1	1	1	0.83	5	1	2
Parker, 2020	0	0	0	2	1	1	0.67	4	0	0
Rifas-Shiman, 2020	1	1	2	2	1	1	1.33	8	2	2
Ruisch, 2018	2	1	0	2	−1	1	0.83	5	2	2
Skovlund, 2017	2	0	2	2	0	1	1.17	7	2	2
Streissguth, 1987	−1	−1	0	0	1	1	0.00	0	0	0
Tovo-Rodriguez, 2020	1	−1	0	2	1	1	0.67	4	0	0
Tronnes, 2020	2	1	0	0	1	1	0.83	5	2	2
Vlenterie, 2016	2	0	0	2	1	1	1.00	6	2	2
Woodbury, 2024	0	0	1	2	1	1	,83	5	1	1
Score study of evidence: +2 – very strong; +1 – strong; 0 – moderate; -1 – weak; -2 – very weak/none										
Before new study	0.87	0.27	0.40	1.40	0.67	1.07	0.77	4.67	1.20	1.40
Average w/ Woodbury-2	0.88	0.25	0.38	1.44	0.63	1.06	0.77	4.63	1.19	1.38

ADHD (pooled relative risk: 1.34) and ASD (pooled relative risk: 1.19), with stronger associations linked to longer duration of exposure. Masarwa et al. suggested the modifying effect of duration of exposure on the association between acetaminophen and neurodevelopmental outcomes can be viewed as suggesting a dose–response effect. Also, Ricci et al. [15] conducted a systematic review and meta-analysis to examine the association between in utero acetaminophen exposure and child neurodevelopmental outcomes. The analysis included 16 studies and used the Systematic Assessment of Quality in Observational Research (SAQORORO)[15] to evaluate quality. They found that prenatal acetaminophen exposure was associated with an increased risk of attention deficit hyperactivity disorder (ADHD) (odds ratio: 1.26), autism spectrum disorder (ASD) (odds ratio: 1.19), and other neurodevelopmental issues such as behavioral and cognitive problems. The risk was higher with longer exposure durations. Although we used a different approach in the Navigation Guide Methodology, the results of these independent literature analyses showed the same direction of association between exposure to acetaminophen and increased risk of abnormal neurodevelopment.

By contrast, an earlier sibling-controlled study by Brandlistuen et al., using the same Norwegian MoBa cohort but with continuous neurodevelopment outcome measures, had a larger sample size (134 discordant pairs) and found significant associations between prenatal acetaminophen and adverse neurodevelopment in the sibling-controlled analyses [50]. The discrepancy in findings may stem from limited power in Gustavson's sibling control analysis. An additional consideration is that while the within-pair estimates are free from confounding by shared factors, they are more susceptible to bias by non-shared confounders compared to unpaired cohort analyses [53].

A third, large prospective cohort study conducted in Sweden by Ahlqvist et al. found that modest associations between prenatal acetaminophen exposure and neurodevelopmental outcomes in the full cohort analysis were attenuated to the null in the sibling control analyses [33]. However, exposure assessment in this study relied on midwives who conducted structured interviews recording the use of all medications, with no specific inquiry about acetaminophen use. Possibly as a resunt of this approach, the study reports only a 7.5% usage of acetaminophen among pregnant individuals, in stark contrast to the ≈50% reported globally [54]. Indeed, three other Swedish studies using biomarkers and maternal report from the same time period, reported much higher usage rates (63.2%, 59.2%, 56.4%) [47]. This discrepancy suggests substantial exposure misclassification, potentially leading to over five out of six acetaminophen users being incorrectly classified as non-exposed in Ahlqvist et al.

Sibling comparison studies exacerbate this misclassification issue. Non-differential exposure misclassification reduces the statistical power of a study, increasing the likelihood of failing to detect true associations in full cohort models – an issue that becomes even more pronounced in the "within-pair" estimate in the sibling comparison [53]. Magnified bias in sibling control comparisons can be attributed to the fact that only sibling pairs discordant on exposure and outcome contribute to "with-in pair" associations. Gustavson et al. used Monte Carlo simulations to assess bias due to measurement error in sibling control models, assuming a true relationship between exposure and outcome. Their findings indicate that decreasing exposure reliability and increasing sibling correlations in the exposure led to deflated exposure-outcome associations and inflated associations between the family mean of the exposure and outcome, increasing the risk of falsely concluding that associations were confounded [63].

Additionally, while sibling comparison studies eliminate the impact of shared family factors that operate as confounders, they also eliminate potential mediators that are shared in families that interact with acetaminophen, potentially introducing bias [64]. Experimental evidence identifies biological mediators of prenatal acetaminophen effects, which may cluster within families. These mechanisms include endocrine disruption [65], increased oxidative stress [66], and alterations in prostaglandin [68], endocannabinoid [70] and neurotransmission systems [35]. A recent simulation study demonstrated that both controlling for mediators and underreporting acetaminophen usage could severely bias neurodevelopmental associations toward the null, reducing the observed effect[72]. Moreover, the Ahlqvist et al. study itself acknowledges bias from carryover effects, where the association with prenatal acetaminophen and ADHD varied based on birth order. The author attributed this to increasing ADHD prevalence over time [73]. In summary, the limitations in data accuracy and methodology cast doubt on the accuracy and reliability of the sibling-controlled studies. The sibling control design may, in fact, introduce bias rather than mitigate it. Thus, caution is warranted in the interpretation of these findings.

On other hand, the observed association between prenatal acetaminophen exposure and NDDs may be hypothesized to follow a 'two-hit' developmental model[74], where acetaminophen acts as the first insult during vulnerable brain maturation windows, and concurrent stressors (e.g., maternal fever, infection, oxidative stress) serve as the second hit. This framework remains speculative, as direct evidence is lacking. Jones

et al. suggest that adjusting for these cofactors without interaction terms attenuates the acetaminophen effect toward the null, indicating potential effect modification rather than confounding[72]. Future epidemiologic studies should pre-specify interaction terms (e.g., acetaminophen × maternal fever) and conduct stratified analyses to test this hypothesis. Until then, we present it transparently, consistent with the precautionary principle[74], to guide mechanistic research and clinical caution. Although currently, available evidence remains limited, integrating this approach could significantly improve methodological designs and the interpretation of future studies on this association, aligning well with the precautionary principle in environmental health promoted by Kriebel et al., which advocates for preventive measures even in the context of scientific uncertainty.

Confounding by indication is a relevant point to our literature analysis. Confounding by indication is a type of bias that may occur in observational studies, particularly in pharmacoepidemiology, where the reason for prescribing a treatment (the indication) is related to the outcome being studied. However, some of the studies evaluated here, explored whether confounding by indication may play some role in the association. For example, Avella-Garcia et al. [28]. included in their study the presence of maternal chronic illness, fever, or urinary tract infections at any time during pregnancy in all models and ran sensitivity analyses excluding mothers with each of these conditions, excluding mothers with any of these, and including exposed mothers by indication (analgesia/infection) to evaluate possible 'within exposure group' variations by indication. Alemany et al. also included analyses adjusted for indications for acetaminophen use [21]. Gustavson et al. also included the sum of the number of days of acetaminophen exposure across all indications, and all questionnaires were calculated for each child [26]. Results showed minimal influence of confounding by indication in these studies.

Experimental studies have shown biological plausibility of a potential adverse effect of acetaminophen on the fetal brain. Acetaminophen freely crosses the placental barrier [58], reaching levels in fetal circulation similar to maternal circulation within less than an hour of maternal ingestion [76]. Acetaminophen undergoes oxidative metabolism via the enzyme CYP2E1—present in fetal brains, placenta, and lungs [78–80]—to produce toxic metabolites [81]. Further, the developing brain is highly susceptible to damaging oxidative stress because it is rapidly growing and maturing and requires significant energy metabolism. Animal models show that prenatal acetaminophen exposure increases oxidative stress markers in the fetal brain and is associated with neurodevelopmental deficits [82]. In addition, acetaminophen also affects prostaglandin and endocannabinoid pathways, which are involved in prenatal neuronal development [84–86]. Importantly, confounding is minimal in well-controlled randomized animal model studies so findings consistent with human studies strengthen causal inference.

During prenatal development, the endocrine system plays a crucial role in brain development, as it regulates the production and activity of hormones that are essential for healthy neurological development. Disruptions to the endocrine system, such as exposure to endocrine-disrupting chemicals, can interfere with the activity of these hormones and potentially lead to permanent structural and functional alterations in the developing brain. Acetaminophen is an endocrine disruptor that directly perturbs hormone-dependent processes, affects neurodevelopment and reproductive disorders, and might alter steroidogenesis in the placenta and induce placental damage. In vivo, in vitro, and ex vivo studies show that acetaminophen directly perturbs hormone-dependent processes [87–89] that are implicated in the development of NDDs [90].

Further, during prenatal development, the epigenome undergoes dynamic changes that regulate gene expression, contributing to brain development [91]. Alterations in the epigenome can alter neural networks critical for normal brain function [93], resulting in abnormal gene expression that may contribute to NDDs [94], Prenatal acetaminophen use is associated with DNA methylation changes in fetal tissues and the placenta, including at loci vital for neurodevelopment [95]. Similar results have been shown in children diagnosed with ADHD exposed to prenatal acetaminophen, with one study suggesting DNA methylation changes in genes involved in oxidative stress, neural transmission, and olfactory sensory pathways [97]. Prenatal acetaminophen exposure of human embryonic stem cells during neuronal differentiation has been shown to induce alterations in transcriptional and epigenetic regulation in early brain development [71], consistent with gene expression changes seen in the brains and placentas of acetaminophen developmentally exposed rodents [99]. A recent human study evaluating RNA sequencing changes from maternal acetaminophen exposure found placental upregulation of immune system pathways in females and downregulation of oxidative phosphorylation in both sexes [17], aligning with earlier transcriptomic results from acetaminophen-exposed mice [99]. Several studies have linked elevated immune response during pregnancy with offspring neurodevelopmental disorders [101]. Additionally, oxidative phosphorylation deficiencies have been associated with adverse neurodevelopmental trajectories [102].

While the majority of studies, particularly prospective cohorts, reported positive associations between prenatal acetaminophen exposure and NDDs, null findings from sibling-controlled studies (e.g., [26]) offer valuable insights. These null results, however, are tempered by methodological challenges, such as exposure misclassification and reduced statistical power, which the Navigation Guide's risk-of-bias assessment identified as limitations. Conversely, positive findings are supported by consistency and biological plausibility, though residual confounding remains a concern. This balanced consideration underscores the need for further research to reconcile these discrepancies.

In interpreting the overall body of evidence, our analysis prioritized studies with robust designs, such as prospective cohorts showing positive associations, while noting methodological limitations in sibling-controlled studies with null findings (e.g., [26]), including power and exposure misclassification. However, we recognize that null or negative associations, whether from sibling designs or conventional cohorts, remain informative and may be underreported due to publication bias. Approximately 80% of the included studies were published post-2013, suggesting a potential time-lag bias favoring positive results. To mitigate selective interpretation, future updates will include sensitivity analyses excluding the top and bottom 10% of studies by quality, ensuring a balanced assessment aligned with the Navigation Guide's standards.

Although a meta-analysis is a valuable tool in systematic reviews, we did not conduct one due to significant heterogeneity across studies in exposure assessment (e.g., maternal self-reports vs. biomarkers), timing and duration of exposure, outcome measures (e.g., ADHD diagnoses vs. behavioral scales), and confounder adjustment approaches. Initial attempts to standardize effect estimates, including those from studies like Liew et al. [27], were deemed unfeasible due to non-comparable formats, risking biased pooled results. Consistent with the Navigation Guide methodology, we prioritized a structured qualitative synthesis and evidence grading to assess causality robustly.

A limitation of this review is the reliance on qualitative assessment of residual confounding within the Navigation Guide framework, which did not incorporate quantitative bias analysis (e.g., E-value or sensitivity analysis beyond basic adjustments). While studies adjusted for key confounders and used sensitivity analyses, unmeasured or residual confounding remains a potential source of bias, particularly for confounding by indication. This highlights the need for future studies to employ quantitative methods to further refine these associations further.

Conclusions

Our analysis demonstrated evidence consistent with an association between exposure to acetaminophen during pregnancy and offspring with NDDs, including ASD and ADHD, though observational limitations preclude definitive causation. This analysis, using the Navigation Guide methodology, synthesizes evidence from several population studies and supports an association between prenatal acetaminophen exposure and increased NDD incidence, including ADHD, ASD, and other NDDs. While population-level trends in NDD rates have risen, potentially due to several factors including improved diagnostics and external exposures, further research is needed to confirm these associations and determine causality and mechanisms. A causal relationship is plausible because of the consistency of the results and appropriate control for bias in the large majority of the epidemiological studies, as well as acetaminophen's biological effects on the developing fetus in experimental studies. Further, a potential causal relationship is consistent with temporal trends—as acetaminophen has become the recommended pain reliever for pregnant mothers, the rates of ADHD and ASD have increased > 20-fold over the past decades[6–108]. While this association warrants caution, untreated maternal fever and pain pose risks such as neural tube defects and preterm birth, necessitating a balanced approach. We recommend judicious acetaminophen use—lowest effective dose, shortest duration—under medical guidance, tailored to individual risk–benefit assessments, rather than a broad limitation.

Abbreviations

ADHD	Attention-Deficit/Hyperactivity Disorder
ADI	Area Deprivation Index
APAP	N-acetyl-p-aminophenol
ASD	Autism Spectrum Disorder
CIs	Confidence Intervals
CYP2E1	Cytochrome P450 2E1
DNA	Deoxyribonucleic Acid
GRADE	Grading of Recommendations Assessment, Development and Evaluation
ISI	Institute for Scientific Information
MoBa	Norwegian Mother, Father and Child Cohort Study
NDDs	Neurodevelopmental Disorders
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
RNA	Ribonucleic Acid
US	United States

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Authors' contributions

AAB: writing, reviewing, discussing, and editing the manuscript; BR: writing, reviewing, discussing, and editing the manuscript; DP: writing, reviewing, discussing, and editing the manuscript. AZB: writing, updating, discussing and editing the manuscript. All authors have read and agreed to the published version of the manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Human ethics and consent to participate
Not applicable.

Competing interests
Dr. Baccarelli served as an expert witness for the plaintiff's legal team on matters of general causation involving acetaminophen use during pregnancy and its potential links to neurodevelopmental disorders. This involvement may be perceived as a conflict of interest regarding the information presented in this paper on acetaminophen and neurodevelopmental outcomes. Dr. Baccarelli has made every effort to ensure that this current work—like his past work as an expert witness on this matter—was conducted with the highest standards of scientific integrity and objectivity.

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